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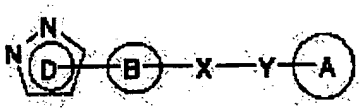
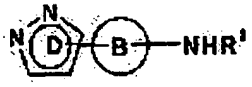
(54) PYRAZOLE DERIVATIVE

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a new pyrazole derivative having an excellent Ca2+ release activated Ca2+ channel(CRACC) inhibiting action and useful for prevention or treatment of inflammatory diseases, allergic diseases, or the like, in which CRACC participates.
SOLUTION: This pyrazole derivative is represented by formula I [D is a pyrazolyl which may be substituted by a substituent group such as a lower alkyl, a lower alkenyl or a lower alkynyl; B is a divalent group of monocyclic aromatic hetero ring which may be substituted by phyenylene, or the like; X is NR1CO (R1 is H, OH, a lower alkyl, or the like), or the like; Y is a bond, CO or the like; A is a phenyl having at least one substituent group such as



I



II

OH or the like], e.g. 4'-[3,5-bis(trifluoromethyl)1H-pyrazol-1-yl]-2,1,3- benzooxadiazol-5-carboxanilide. The compound of formula I can be obtained by subjecting, e.g. an amine derivative of formula II to amidation reaction with a carboxylic acid derivative of formula III.

LEGAL STATUS

[Date of request for examination]

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* NOTICES *

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2.**** shows the word which can not be translated.
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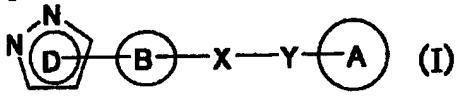
CLAIMS

[Claim(s)]
[Claim 1] The pyrazol derivative shown by the general formula (I), or its salt permitted pharmaceutically.
[Formula 1]



(I)

(The notation in a formula expresses following semantics.)
D: - low-grade alkyl, - low-grade alkenyl, - low-grade alkynyl, - halogeno low-grade alkyl, - Low-grade alkylene-cycloalkyl, - low-grade alkylene-O-low-grade alkyl, - The pyrazolyl which may have 1-3 substituents chosen from the group which consists of cycloalkyl, -O-low-grade alkyl, -COOH, and -COO-low-grade alkyl and a - halogen atom, B : Phenylene or the divalent radical of the monocyclic aromatic compound heterocycle which may be permuted by low-grade alkyl, X: -NR1-CO-, -CO-NR1-, -NR1-SO2-, or -SO2-NR1-R1:-H, - OH, - low-grade alkyl, -O-low-grade alkyl, or -CO-low-grade alkyl, Y: -- association, -CO-, and - low-grade alkylene - or - low-grade ARUKENIREN - A: The phenyl which has at least one substituent chosen from -OH, -O-low-grade alkyl, and -F, Or when the monocycle which may have the substituent or 2 thru/or 3 ring type condensation hetero aryl, however Y are association A shows radicals other than the hetero aryl chosen from the thienyl and pyrrolyl which may be permuted by low-grade alkyl, imidazolyl, thiazolyl, oxazolyl, thiadiazolyl, pyridyl, pyrazinyl one, and iso quinolyl.
[Claim 2] The remedy which makes an active principle a pyrazol derivative or its salt permitted pharmaceutically according to claim 1.
[Claim 3] The calcium bleedoff dependency calcium channel inhibitor which makes an active principle a pyrazol derivative or its salt permitted pharmaceutically according to claim 1.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to a calcium bleedoff dependency calcium channel inhibitor useful for the prevention or the therapy of a remedy, an inflammatory disease, an allergic disease, etc. in which a calcium bleedoff dependency calcium channel participates especially.
[0002]
[Description of the Prior Art] For many years, the importance of calcium ion (calcium2+) is known as an intracellular transfer mechanism in various cell activation. An inflammatory cell does not leak to an exception, either but intracellular calcium2+ is functioning as an important regulator. However, membrane potential dependency calcium2+ channel (it outlines Following VOCC) inhibitor, such as nifedipine conventionally known as a calcium2+ antagonist, did not show depressant action to inflammatory cell activation, but it was suggested to the inflammatory cell that calcium2+ inflow mechanisms other than VOCC exist. Hoth and others has reported that the calcium2+ inflow mechanism (; outlined below calcium2+release activated calcium2+channel; CRACC -- called a calcium store dependency calcium channel (store-dependent calcium2+channel)) from the outside of an alternative cell, i.e., a calcium bleedoff dependency calcium channel, exists in calcium2+ caused by calcium2+ store exhaustion in a mast cell or a lymphocyte. Furthermore, the mast cell and the lymphocyte have also reported that it is an insusceptibility to membrane potential (Pflugers Arch., 430, and p315-22 (1995)). CRACC A mast cell, a lymphocyte, astrocytic (J.Biol.Chem., 270, and p29-32) (1995), etc., Existing in almost all inflammatory cells is known, and it gets down. It turns out that it is participating in cytokine production, lipid mediator isolation, etc. deeply (J.Immunol., 155, p285-96 and (1995) Br.J.Pharmacol., 144, and p598-601 (1995)).
[0003] Recent years come, and since it was shown clearly that CRACC inhibition activity was in one of the action mechanisms of the tenidap (tenidap) which is an arthritis-chronica rheumatism therapy agent, (Cell Calcium 14 and p1-16 (1993)) and CRACC inhibitor may show clinical usefulness to chronic-inflammation diseases, such as rheumatoid arthritis. Moreover, it is known that CRACC exists also in an endothelial cell (Am.J.Physiol., 269, and C 733-8) and (1995) an epithelial cell (J.Biol.Chem., 270, and p169-75 (1995)). In case an endothelial cell receives a radical failure, it is reported that the continuous calcium entry is involving (Am.J.Physiol., 261, and C 889-896 (1991)), and it is suggested that CRACC inhibitor has a protective action to the organization failure in which an endothelial cell participates.
[0004] Furthermore, controlling production of that calcium entry inhibition has the depressant action of cell proliferation and interleukin 2 (IL-2) is also reported (Br.J.Pharmmacol., 133, and p861-8 (1994)), and CRACC inhibitor is useful as a prevention / therapy agent of fecundity or progressive diseases, such as a malignant tumor, and an autoimmune disease, and useful also as an inhibitor of the rejection at the time of transplantation. On the other hand, as for the excitable cell represented by a smooth muscle cell and the nerve cell, intracellular calcium accommodation is performed by VOCC, and it is known that CRACC will not involve. Therefore, it is expected that the calcium channel inhibitor which has CRACC selectivity to VOCC will turn into drugs useful for prevention or the therapy of the various inflammatory diseases which show the operation which is not desirable to neither a blood vessel smooth muscle nor the central nerves, an allergic disease, tissue damage, a fecundity disease, etc. Some compounds which have CRACC inhibitory action are reported in recent years, for example, 2-(3, 4-dihydro-1-iso quinolyl) acetamido derivative is

indicated for the cycloalkyl-piperazinyl ethanol derivative by WO 94/No. 00435 official report at the German disclosure No. 4404249 official report. moreover -- reference (J.Pharm.Exp.Ther., 257, and p967-971) (1991) -- 5-amino-1-[[5[3 and]-dichloro-4-(4-chloro benzoyl) phenyl] methyl]-1H- it is indicated that the 1, 2, and 3-triazolo-4-carboxamide has CRACC inhibitory action.

[0005]

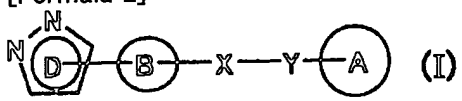
[Problem(s) to be Solved by the Invention] However, the compound with which reference is not made at all about the selectivity of the compound which has the CRACC inhibitory action reported conventionally, but the CRACC selectivity over VOCC is checked is not reported yet. Therefore, it is anxious for the invention of the high drugs of CRACC selectivity to the CRACC inhibitor which excels [therapy / of various inflammatory diseases, an allergic disease, tissue damage, a fecundity disease, etc. / prevention or the therapy] in useful effectiveness, especially VOCC.

[0006]

[Means for Solving the Problem] this invention person etc. looks for the compound which has CRACC inhibitory action previously, and has the CRACC inhibitory action excellent in the pyrazol derivative which completely differs in structure with the CRACC inhibitor of the conventional known, and performed header application for the CRACC selectivity over VOCC being good (PCT application number JPs 98/04583). When this invention person etc. introduced into this pyrazol derivative further various substituents (radical shown by -Y-A among the following general formula) and that CRACC inhibitory action was considered, the compound shown by the following general formula (I) completed a header and this invention for having the more excellent CRACC inhibitory action.

[0007] namely, the new pyrazol derivative in which this invention is shown by the following general formula (I) or its salt permitted pharmaceutically, and the remedy which contains these in a list as an active principle -- it is especially related with a calcium bleedoff dependency calcium channel (CRACC) inhibitor.

[Formula 2]



(I)

(The notation in a formula expresses following semantics.)

D: - low-grade alkyl, - low-grade alkenyl, - low-grade alkynyl, - halogeno low-grade alkyl, - Low-grade alkylene-cycloalkyl, - low-grade alkylene-O-low-grade alkyl, - The pyrazolyl which may have 1-3 substituents chosen from the group which consists of cycloalkyl, -O-low-grade alkyl, -COOH, and -COO-low-grade alkyl and a - halogen atom, B : Phenylene or the divalent radical of the monocyclic aromatic compound heterocycle which may be permuted by low-grade alkyl, X: -NR1-CO-, -CO-NR1-, -NR1-SO2-, or -SO2-NR1-R1:-H, - OH, - low-grade alkyl, -O-low-grade alkyl, or -CO-low-grade alkyl, Y: -- association, -CO-, and - low-grade alkylene - or - low-grade ARUKENIREN - A: The phenyl which has at least one substituent chosen from -OH, -O-low-grade alkyl, and -F, Or when the monocycle which may have the substituent or 2 thru/or 3 ring type condensation hetero aryl, however Y are association A shows radicals other than the hetero aryl chosen from the thienyl and pyrrolyl which may be permuted by low-grade alkyl, imidazolyl, thiazolyl, oxazolyl, thiadiazolyl, pyridyl, pyrazinyl one, and iso quinolyl. the following -- the same .

[0008]

[Embodiment of the Invention] Hereafter, this invention is explained to a detail. In addition, in this application description, "-Alk" and "low-grade alkylene" are written as "-Alk -", and a "halogen atom" is written for "low-grade alkyl" as "-Hal." Unless it refuses especially with "it is low-grade" among this description, the straight chain which has a carbon number 1 thru/or six pieces, or the chain of the letter of branching is meant. As "low-grade alkyl", methyl, ethyl, propyl, etc. have desirable ethynyl vinyl, 1-propenyl, 1, and 2-dimethyl-1-propenyl etc. as "low-grade alkynyl" as "low-grade alkenyl" again. Moreover, as "low-grade alkylene", methylene and ethylene are desirable. As a "halogen atom", they are I, Br, F, and Cl. As "halogeno low-grade alkyl", it is the low-grade alkyl permuted by one or more halogen atoms, and is trifluoromethyl especially preferably. As "aryl", it is a carbon number 6 thru/or 14 aryl groups, and they are phenyl and naphthyl preferably. As "cycloalkyl", it is a carbon number 3 thru/or eight cycloalkyl, and is KISHIRU in cyclo propyl and cyclo preferably.

[0009] As "phenylene", it is 1 and 4-phenylene preferably. As "a divalent radical of monocyclic

aromatic compound heterocycle", it is the divalent radical of 1 5 contained four pieces thru/or 6 member monocyclic aromatic compound heterocycle about the hetero atom chosen from N, S, and O atom, and they are a furan -2, 5-diyl, a thiophene -2, 5-diyl, a thiazole -2, 5-diyl, a pyridine -2, 5-diyl and a pyrimidine -2, and 5-diyl preferably. As "a monocycle or 2 thru/or 3 ring type condensation hetero aryl", they are 1 5 included five pieces thru/or 7 member monocycle or 2 thru/or 3 ring type condensed-ring hetero aryl about O, S, or N atom as a hetero atom. Preferably Thienyl, a furil, pyrrolyl, imidazolyl, pyrazolyl, Thiazolyl, iso thiazolyl, oxazolyl, isoxazolyl, tetra-ZORIRU, Thoria ZORIRU, thiadiazolyl, pyridyl, pyrazinyl one, pyrimidinyl, Pilus DAJINIRU, pyranyl, the indolyl, the iso indolyl, benzofuranyl, Benzoimidazolyl, benzothienyl, benzothoria ZORIRU, bends thiadiazolyl, Benzooxadiazolyl, benzodioxo RANIRU, iso quinolyl, quinolyl, They are kino KISANIRU, phthalazinyl, chinae-cortex ZORINIRU, naphthyridinyl, SHINNORINIRU, clo MENIRU, imidazo [1 and 2-a] pyridyl, [2 and 3-pyrazino d] pilus DAJINIRU, 4H-imidazo [4 and 5-d] thiazolyl, and pyrrolo [2 and 3-b] pyridyl. As a radical by which these radicals may be hydrogenated selectively and partial hydrogenation was carried out Preferably Pyrroline, imidazoline, pyrazoline, dihydropyridyl, Tetrahydropyridyl, dihydropyrimidinyl, dihydropilus DAJINIRU, In DORINIRU, tetrahydro quinolyl, dihydrokino KISARINIRU, 2, 3 and 4, 5-tetrahydro-1H-1, 4-benzodiazepinyl, 1, 4-dihydro-2H-3, 1-benzoxazinyl, 4, 5 and 6, 7-tetrahydro benzofuranyl one, etc. are mentioned.

[0010] such hetero aryls -- the substituent of arbitration -- 1 thru/or five pieces -- having -- **** -- as this substituent -- desirable -Alk, - low-grade alkenyl, - low-grade alkynyl, -Hal, and -NR-Alk-NR'R" (R, R', and R" mean -H or -Alk here, respectively.) the following -- the same . - NR- (nitrogen-containing saturation ring which may be permuted by -Alk) -- - NR-Alk- (-nitrogen-containing saturation ring which may be permuted by Alk), - NR- (cycloalkyl which may be permuted by -NR'R"), - NR'R", -NO2, -CN, -OH, -O-Alk, -O-CO-Alk, - SH, -S-Alk, =O, -COOH, -COO-Alk, -CO-Alk, - CHO, -CO-NR'R", -SO-Alk, -SO2-Alk, - SO2-NR'R", - (-nitrogen-containing saturation ring which may be permuted by Alk), - The aryl which may have the substituent, the aryl which may have the -O-substituent, - The monocycle hetero aryl which may have the substituent, the monocycle hetero aryl which may have the -O-substituent, - Cycloalkyl, -O-cycloalkyl which may be permuted by -NR'R", - It is the substituent chosen from halogeno low-grade alkyl, -O-halogeno low-grade alkyl, -Alk-NR'R", and -Alk- (nitrogen-containing saturation ring which may be permuted by -Alk) and the group which consists of -Alk-OH.

[0011] Here, as a "nitrogen-containing saturation ring", it is 1 5 which may include two pieces and may contain O or one S atom further thru/or 8 member nitrogen-containing saturation heterocycle about N atom, and the unsaturated bond may be selectively included as a ring atom, or you may condense with the benzene ring. Preferably, they are pyrrolidinyl, imidazolidinyl, PIRAZORIJINIRU, piperidyl, piperazinyl one, gay piperazinyl, mol HORINIRU, perhydro-1,4-thiazinyl, tetrahydropyridyl, 1, 2 and 3, and 4-tetrahydro iso quinolyl. As "monocycle hetero aryl", the monocycle hetero aryl under above "a monocycle or 2 thru/or 3 ring type condensation hetero aryl" is mentioned. Moreover, as a substituent in "the aryl which may have the substituent", and "the monocycle hetero aryl which may have the substituent", -Alk, -Hal, -NR'R", - halogeno low-grade alkyl and -NO2, -CN, -OH, -O-Alk, -SH, -S-Alk, -COOH, -COO-Alk, -CO-Alk, etc. are mentioned. "The phenyl which has at least one substituent chosen from -OH, -O-low-grade alkyl, and -F" may have these at least one substituents, and may have the 1-4 still more nearly same substituents as the above "the aryl which may have the substituent." Moreover, when Y is association, X and A couple directly. As a desirable compound of the general formula (I) of this invention, the pyrazolyl radical of D is 1H-pyrazole-5-IRU, 1H-pyrazole-3-IRU, or 1H-pyrazole-1-IRU, and is the pyrazolyl permuted by 1-2 trifluoromethyl radicals, the pyrazol derivative which is 3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU especially, or its salt permitted pharmaceutically still more preferably. As X, -NHCO- has [1 and 4-phenylene] association desirable [moreover,] as B especially as Y. Although a geometrical isomer and a tautomer may exist depending on the class of substituent of this invention, the thing which these isomers separated, or mixture is included by this invention. Moreover, this invention compound may have an asymmetric carbon atom, and the optical isomer of the (R) object based on this and the (S) object may exist. This invention includes all of the mixture and the isolated thing of these optical isomers.

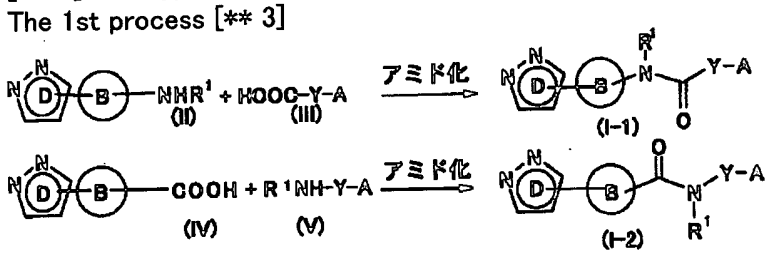
[0012] this invention compound (I) may form a salt with a base depending on the class of an acid addition salt or substituent. As this salt, it is the salt permitted pharmaceutically. Preferably Inorganic acids, such as a hydrochloric acid, a hydrobromic acid, a hydroiodic acid, a sulfuric acid, a nitric acid, and a phosphoric acid, A formic acid, an acetic acid, a propionic acid, oxalic acid, a

malonic acid, a succinic acid, boletic acid, A maleic acid, a lactic acid, a malic acid, a tartaric acid, a citric acid, methansulfonic acid, An acid addition salt with organic acids, such as ethane sulfonic acid, an aspartic acid, and glutamic acid, Salts, ammonium salt, etc. containing metals, such as sodium, a potassium, magnesium, calcium, and aluminum, with an organic base, such as an inorganic base, monomethylamine, ethylamine, ethanolamine, a lysine, and an ornithine, are mentioned. Furthermore, this invention also includes the matter of this invention compound (I), various kinds of hydrates of the salt and solvate, and a crystal polymorphism.

[0013] (Manufacturing method) this invention compound and its salt permitted pharmaceutically can use the basic frame or the description based on the class of substituent, and can manufacture it with the application of various well-known synthesis methods. Depending on the class of functional group, a raw material thru/or a protective group suitable in the phase of intermediate field, i.e., transpose to the radical which can be converted into the functional group concerned easily, may be effective on a manufacturing technology in the functional group concerned in that case. A protective group can be removed the appropriate back if needed, and a desired compound can be obtained. What is necessary is to be able to mention a hydroxyl group, a carboxyl group, etc. as such a functional group, to be able to mention the protective group of Green (Greene) and the Wuts (Wuts) work, "Protective Groups in Organic Synthesis", and the 2nd-edition publication as those protective groups, and just to use these suitably according to a reaction condition.

[0014] The typical manufacturing method of this invention compound is explained below.

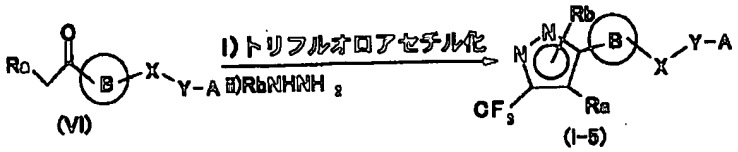
The 1st process [** 3]



[0015] This process is this invention compound (I-1) or (I-2) the approach of acquiring by giving the carboxylic-acid derivative expressed with the amine derivative and general formula (III) which are expressed with a general formula (II) or (V), or (IV) to an amidation reaction, as shown in said reaction formula. The activity ester; symmetry acid anhydride which the carboxylic-acid derivative (III) which can be used in this 1st process, or (IV) is an isolation carboxylic acid or its reactant derivative, and can be prepared, for example, using acid halide; acid azide; methanols, such as an acid chloride and acid bromide, ethanol, benzyl alcohol, the phenol that may be permuted, 1-hydroxy benzotriazol, N-hydroxysuccinimide, etc. as a reactant derivative; a mixed acid anhydride with alkyl carbonic acid, p-toluenesulfonic acid, etc. is mentioned. These reactant derivatives can be manufactured with a conventional method, using a commercial thing. When reacting an isolation carboxylic acid, it is KISHIRU carbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (WSCD), and O-benzotriazol-1-IRU to N and N'-JISHIKURO in the case of a reaction. - It is desirable N, N, N', and to make it react to the bottom of existence of condensing agents, such as N'-tetramethyl URONIUMU hexafluoro phosphate (HBTU). Depending on the case, additives, such as N-hydroxysuccinimide (HONSu) and 1-hydroxy benzotriazol (HOBt), may be added. These amidation reactions can be performed with a conventional method.

[0016] A reaction is performed [derivative / which is expressed with the amine derivative and general formula (III) which are expressed with a general formula (II) or (V), or (IV) / carboxylic-acid] in equimolar or one side in solvents, such as **** for excessive amounts, an organic solvent inactive for a reaction, for example, a pyridine, a tetrahydrofuran (THF), dioxane, the ether, benzene, toluene, dichloromethane, 1,2-dichloroethane (DCE), chloroform, N.N-dimethylformamide (DMF), ethyl acetate, and an acetonitrile. Reaction temperature is suitably chosen by the class of reaction derivative. It may be advantageous to add bases, such as triethylamine, a pyridine, picoline, N.N-dimethylaniline, potassium carbonate, and a sodium hydroxide, depending on the class of reactant derivative, when promoting a reaction. A pyridine can also serve as a solvent.

[0017] The 2nd process [** 4]



(Ra and Rb show H or Alk among a formula.)
This process is an approach of obtaining this invention compound (I-3), by making it react with a hydrazine derivative and cyclizing, after trifluoroacetylating the carbon atom which adjoins the ketone of the compound expressed with a general formula (VI). It can perform trifluoroacetylating [of the 1st process] by making trifluoroacetylating agents (for example, ethyl trifluoro acetate, anhydrous trifluoroacetic acid, etc.) react under heating reflux from -78 degrees C among solvents, such as a methanol, ethanol, 1, 3-dimethyl imidazolidine-2-ON (DMI), and THF, DMF, under existence of bases, such as sodium methoxide, a sodium ethoxide, alkali-metal hexa methyl JISHIRAJIDO, an alkali-metal hydride, alkyl lithium, and triethylamine. The ring closure of the 2nd process can perform the compound and hydrazine derivative which were obtained at the 1st process by making it react with the inside of solvents, such as a methanol and ethanol, or a non-solvent under existence of Lewis acid, such as acids, such as an acetic acid and a hydrochloric acid, or titanium (IV) isopropanal POSHIKIDO, titanium (IV) chloride, and a boron trifluoride-diethylether complex, or nonexistence. This reaction can be performed under cooling thru/or heating reflux.
[0018] this application compound whose X is -SO2-NR1- or -NR1-SO2- can be replaced with a carboxylic-acid derivative, and can be manufactured like said 1st process except using a sulfonic-acid derivative. In N-alkylation of the nitrogen atom of the amino group of X or an amide group, and a list, N-alkylation of a ring nitrogen atom N-alkylation of a conventional method, for example, an amine derivative, and the alkyl compound which has leaving groups in ordinary use, such as a halogen atom or organic sulfone residue It can carry out by reacting in inert solvents, such as DMF, an acetone, 2-butanone, and an acetonitrile, under existence of bases, such as potassium carbonate, triethylamine, and a sodium hydride, or nonexistence, and making it react under cooling thru/or reflux with a non-solvent. Moreover, in addition to this, clearance of a protective group etc. can be performed in installation of the substituent to each ring, and the qualification list of a radical with a conventional method.
[0019] (Process of a raw material compound) The raw material compound of the above-mentioned manufacturing method is marketed, or can be easily compounded by the well-known approach to this contractor. For example, some raw material compounds of this invention compound are indicated by PCT application (JPs 98/04583) with the manufacturing method, and it can also manufacture other raw material compounds according to the same manufacturing method.
[0020] The resultant acquired by each above-mentioned process is isolated as an isolation compound, its salt, a hydrate, or various kinds of solvates, and is refined. A salt can be manufactured by giving the usual salt formation reaction. Isolation and purification are performed with the application of the usual chemistry actuation, such as an extract, concentration, distilling off, crystallization, filtration, recrystallization, and various chromatographies. Various isomers can be isolated with a conventional method using the physicochemical difference between isomers. For example, an optical isomer is separable with a general optical resolution method, for example, fractional-crystallization-izing, or a chromatography. Moreover, an optical isomer is also compoundable from a suitable optical activity raw material compound.
[0021]
[Effect of the Invention] this invention compound is useful as an active ingredient of a remedy constituent. It has CRACC inhibitory action and IL-2 production depressant action especially, and is useful as a CRACC inhibitor or an IL-2 production inhibitor. It is useful as allergic [in which CRACC and IL-2 production participate especially], inflammatory, or a prevention therapy agent of an autoimmune disease. Here, as allergic, inflammatory, or an autoimmune disease, various diseases in which CRACC or IL-2 production participates, such as bronchial asthma, psoriasis, an atopic disease including atopic dermatitis, an inflammatory bowel disease including Crohn's disease, a peptic ulcer, a nephritis, hepatitis, pancreatitis, a collagen disease, articular rheumatism, hypertrophic arthritis, and rejection at the time of transplantation, are included.
[0022] On the other hand, since a CRACC inhibitor has the depressant action to cell proliferation,

it is useful for prevention or the therapy of fecundity, such as a malignant tumor, arteriosclerosis, multi-organ sclerosis, various fibrosing diseases, and keloid in a burn, or a progressive disease. Moreover, the protective action to organization injury, such as an ischemia reperfusion injury, a craniocerebral trauma, cerebral infarction, and myocardial infarction, is also expected from a CRACC inhibitor controlling activation of the cell which participates in an inflammatory response in tips or central organizations, such as a mast cell, an inflammatory cell, or astrocytic one.

[0023] Hereafter, the trial for proving the pharmacological action of this invention compound and a result are shown.

(1) 100micro of CRACC inhibitory action calcium directions fluorochrome fura-Jurkat cell (6x106-/ml) suspension I which loaded 2 (1microM) -- each -- a well -- it poured distributively to inside - microplate was prepared 96 wells. 100micro of Hanks balanced salt solutions I with which calcium pump inhibitor (SAPUSHIGARUGIN) stimulus intracellular calcium concentration lifting contains the test drug and 2microM SAPUSHIGARUGIN (the last concentration, 1microM) of 2 double concentration of the last concentration -- each -- it caused by adding to a well and the fluorescence intensity ratio (R) was computed from two fluorescence intensity obtained by the excitation wavelength of 340nm / 500nm, and the excitation wavelength of 380nm / 500nm after [of addition] 30 minutes. At the time of this fluorescence intensity ratio calculation, own private fluorescence of a test drug was measured by the same approach using the system in which a cell does not exist in advance, and the effect to fura-2 fluorescence by private fluorescence was amended.

[0024] Intracellular calcium concentration is the maximum reaction fluorescence intensity ratio (Rmax) obtained by 25microM ionomycin stimulus and 5microM ionomycin +1mM. It asked from the formula with the fluorescence effectiveness (Sf2) of the calcium dissociation coloring matter at the time of fluorescence effectiveness (Sb2) row excitation wavelength the excitation of 380nm of the minimum reaction fluorescence intensity ratio (Rmin) obtained by the EGTA stimulus and the calcium joint coloring matter at the time of excitation wavelength excitation of 380nm.

formula: -- the intracellular calcium concentration under each concentration test drug existence =224x[intracellular calcium concentration (nM)] [(R-Rmin)/(Rmax-R)] x [Sf2/Sb2] searched for, and a solvent -- the concentration (IC50 value) which shows 50% of CRACC inhibition from the intracellular calcium concentration of the control group called for more independently in quest of the rate intracellular [by each concentration test drug] of calcium entry inhibition (CRACC inhibition) was computed. this invention compound has good CRACC inhibition activity, and had IC50 value below 1microM in the desirable compound.

[0025] (2) 100micro of selectivity calcium directions fluorochrome fura-PC12-h5 rat neuroblast (2x106-/ml) suspension I to VOCC inhibitory action which loaded 2 (1microM) -- each -- a well - - it poured distributively to inside -- prepare - microplate 96 wells. high concentration potassium chloride stimulus intracellular calcium concentration lifting -- the test drug of 2 double concentration of the last concentration, and 100mM(s) 100micro of Hanks balanced salt solutions I containing KCl (the last concentration, 50mM) -- each -- it causes by adding to a well and a fluorescence intensity ratio (R) is computed from two fluorescence intensity obtained by the excitation wavelength of 340nm / 500nm, and the excitation wavelength of 380nm / 500nm after [of addition] 20 minutes. At the time of this fluorescence intensity ratio calculation, own private fluorescence of a test drug is measured by the same approach using the system in which a cell does not exist in advance, and the effect to fura-2 fluorescence by private fluorescence is amended. Like said CRACC inhibitory action, IC50 value of VOCC inhibitory action is computed and it compares with CRACC inhibitory action.

(3) Use an IL-2 production inhibitory action Jurkat cell, and it is S.Clare Chung etc. The approach of Br.J.Pharmacol. and 113:861 -868 (1994) publication is followed, and it is IL-2. Production inhibition activity was examined and the IC50 value was calculated. IC50 value of the desirable compound of this invention was below 0.1microM.

[0026] The remedy which makes an active principle this invention compounds (I) or these salts that are permitted pharmaceutically can be prepared by the approach usually used using one sort of general formulas (I) or these salts that are permitted pharmaceutically or two sorts or more, the support for drugs usually used for pharmaceutical preparation-ization and an excipient, and other additives. Administration may be which gestalt of the parenteral administration by injections, such as internal use by a tablet, a pill, a capsule, the granule, powder, liquids and solutions, inhalations, etc. or intravenous injection, and intramuscular injection, suppositories, ophthalmic solutions, an

eye ointment, the liquids and solutions for transderma, the ointment, the patches for transderma, permucosal liquids and solutions, permucosal patches, etc.
[0027] A tablet, powder, a granule, etc. are used as a solid-state constituent for internal use by this invention. In such a solid-state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, a lactose, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate. The constituent may contain a solubilizing agent like additives other than an inactive diluent, for example, lubricant like magnesium stearate and disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like a lactose, glutamic acid, or an aspartic acid according to a conventional method. The coat of a tablet or the pill may be carried out as occasion demands with the film of glycocalyx, such as cane sugar, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, stomach solubility, or the enteric matter.
[0028] The liquid constituent for internal use contains the inactive diluent generally used, for example, purified water, and ethanol including the opacifier permitted in drugs, a solution agent, suspension, syrups, elixirs, etc. This constituent may contain a wetting agent, an adjuvant like suspension, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent. As injections for parenteral administration, the sterile solution agent of aquosity or nonaqueous nature, suspension, and an opacifier are contained. As a water solution agent and suspension, distilled water for injection and a physiological salt solution are contained, for example. As the solution agent of nonaqueous solubility, and suspension, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (trade name), etc., for example. Such a constituent may also contain an adjuvant still like antiseptics, a wetting agent, an emulsifier, a dispersant, a stabilizing agent (for example, lactose), and a solubilizing agent (for example, glutamic acid, an aspartic acid). These are sanitized by the combination or the exposure of filtration and a germicide which lets for example, a bacteria hold filter pass. These manufacture a sterile solid-state constituent again, and they can also use it for non-bacterial water or the sterile solvent for injection before an activity, dissolving. a pernasal agent etc. -- passing -- as a membrane agent -- the thing of the shape of a solid-state, a liquid, and a semisolid -- it is -- the very thing -- it can manufacture according to a well-known approach. For example, it is added suitably and well-known pH regulator, antiseptics, a thickener, and an excipient are fabricated a solid-state, a liquid, or in the shape of a semisolid. A pernasal agent is prescribed for the patient using the usual spray instrument, a rhinenchysis container, a tube, a nasal cavity interpolation close implement, etc. Usually, in internal use, 0.01 - 20 mg/kg is preferably suitable for the dose on the 1st 50 mg/kg from per [0.001 / about] weight, and it is 1 time or prescribes this for the patient in 2 thru/or 4 steps. When vein administration is carried out, the dose on the 1st is suitable, and per [0.001 / about] weight to 10 mg/kg divides it into 1 time per thru/or plurality day, and prescribes it for the patient. Per [0.001 / about] weight to 50 mg/kg is suitable for the dose on the 1st, in pernasal administration, it divides into 1 time per thru/or plurality day, and it prescribes it for the patient. A dose is suitably determined according to each case in consideration of a symptom, age, sex, etc.
[0029]
[Example] Hereafter, based on an example, this invention is further explained to a detail. this invention compound is not limited to a compound given in the following example.
2, 1, and 3-benzoxadiazole-5-carbonyl chloride (11mg) and triethylamine (8mg) were added to the mixture of an example 14-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] aniline (15mg) and dichloromethane (0.5ml) one by one, and it stirred at the room temperature for 8 hours and 30 minutes. After adding dichloromethane to reaction mixture, sequential washing was carried out with 1 convention sodium-hydroxide water solution, 1 convention hydrochloric acid, and saturation brine. the bottom of the reduced pressure after drying an organic layer with sulfuric anhydride magnesium -- condensing -- 4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] - 2, 1, and 3-benzoxadiazole-5-carboxanilide was obtained.
Thiophene-2-carbonyl chloride (11mg) was added to the mixture of an example 24-[3 and 5-bis (trifluoromethyl)-1H-pyrazole-1-IRU] aniline (7mg) and a pyridine (1ml), and it stirred at the room temperature all night. After adding dichloromethane to reaction mixture, 1 convention sodium-hydroxide water solution washed. After filtering an organic layer using the PTFE filter tube made from Whatman, it condensed under reduced pressure of filtrate and 4'-[3 and 5-bis (trifluoromethyl)-1H-pyrazole-1-IRU] thiophene-2-carboxanilide was obtained.

[0030] Oxalyl chloride (0.92ml) and DMF (0.001ml) were added to an example 33, a 5-dimethyl isoxazole-4-carboxylic acid (1.35g), and the mixture of dichloromethane (15ml) one by one, and it stirred at the room temperature for 4 hours and 30 minutes. After adding toluene (5ml) to the residue condensed and obtained under reduced pressure of reaction mixture, it condensed under reduced pressure. The obtained residue was added to 4-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] aniline (2.02g), triethylamine (1.5ml), and the mixture of dichloromethane (20ml) under ice-cooling, and was stirred at the room temperature for 2 hours. After adding triethylamine (0.95ml) to reaction mixture, it stirred at the room temperature all night. Reaction mixture was ice-cooled, and after adding the mixture of 3 stirred at the room temperature for 3 hours, a 5-dimethyl isoxazole-4-carboxylic acid (386mg), oxalyl chloride (0.22ml), dichloromethane (4ml), and DMF (0.001ml), it stirred for four days at the room temperature. After adding triethylamine (0.95ml) to reaction mixture, it stirred at the room temperature further all night. Ethyl acetate (200ml) was added to reaction mixture, and sequential washing was carried out with water, a saturation sodium-hydrogencarbonate water solution, and saturation brine. After drying an organic layer with sulfuric anhydride magnesium, it condensed under reduced pressure. The obtained solid-state was ******ed from the mixed solvent of ethanol and water, and 3 and 5-dimethyl-4'-[3 and 5-bis (trifluoromethyl)-1H-pyrazole-1-IRU] isoxazole-4-carboxanilide (2.14g) were obtained as fine brown ******.
Thionyl chloride (0.005ml) was added to an example 45-fluoro Indore-2-carboxylic acid (11mg), a pyridine (0.007ml), and the mixture of DMF (0.0005ml) and THF (0.2ml) under ice-cooling, and it stirred for 30 minutes at the room temperature. The pyridine (0.2ml) solution of 4-[3 and 5-bis (trifluoromethyl)-1H-pyrazole-1-IRU] aniline (15mg) was added to reaction mixture, and it stirred at the room temperature for 5 hours. After adding ethyl acetate to reaction mixture, sequential washing was carried out with 1 convention sodium-hydroxide water solution and saturation brine. After drying an organic layer with sulfuric anhydride magnesium, it condensed under reduced pressure and 5-fluoro-4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU]-1H-Indore-2-carboxanilide was obtained.
[0031] The isonicotinic acid (1.17g) and the WSCD hydrochloride (1.82g) were added to the mixture of an example 54-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] aniline (2.00g) and ethyl acetate (20ml) one by one under ice-cooling, and it stirred at the room temperature for 2 hours. Ethyl acetate (10ml) was added to reaction mixture, and it stirred at the room temperature all night. After adding THF (10ml) to reaction mixture and stirring at a room temperature for 5 hours and 30 minutes, the isonicotinic acid (0.50g) and the WSCD hydrochloride (0.78g) were added, and it stirred for two days at the room temperature further. After adding HOBt (0.28g) to reaction mixture and stirring at 40 degrees C for 5 hours and 30 minutes, the isonicotinic acid (1.67g) and the WSCD hydrochloride (2.60g) were added, and it stirred for three days at the room temperature further. Water (100ml) was added to reaction mixture, and ethyl acetate extracted the product. Sequential washing of the extract was carried out with water, a saturation sodium-hydrogencarbonate water solution, and saturation brine, and after drying an organic layer with sulfuric anhydride magnesium, it condensed under reduced pressure. After dissolving the obtained residue in ethyl acetate (30ml) and adding a 4 convention hydrochloric-acid-ethyl-acetate solution (5ml), it condensed under reduced pressure. The obtained solid-state was ******ed from the mixed solvent of ethanol and an acetonitrile, and the 4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] iso nicotine anilide hydrochloride (1.94g) was obtained as yellow color powder-like **.
[0032] The WSCD hydrochloride (1.43g) was added to an example 64-[3 and 5-bis (trifluoromethyl)-1H-pyrazole-1-IRU] aniline (2.00g), a 2-chloro-4-methyl nicotinic acid (1.20g), and the mixture of DMF (20ml) under ice-cooling, and it stirred at the room temperature for 20 hours. After adding the WSCD hydrochloride (0.72g) to reaction mixture under ice-cooling and stirring at a room temperature for 4 hours, the 2-chloro-4-methyl nicotinic acid (0.30g) was added under ice-cooling, and it stirred for one day at the room temperature further. After adding the WSCD hydrochloride (0.72g) to reaction mixture under ice-cooling and stirring for one day at a room temperature, a WSCD hydrochloride (1.43g), HOBt (1.10g), and a 2-chloro-4-methyl nicotinic acid (1.20g) were added, and it stirred for three days at the room temperature further. Water (100ml) was added to reaction mixture, and ethyl acetate extracted the product. Sequential washing of the extract was carried out with water, 1 convention hydrochloric acid, water, and saturation brine, and after drying an organic layer with sulfuric anhydride magnesium, it condensed under reduced pressure. After the silica gel column chromatography (dichloromethane: the 1st

eluate; n-hexane : ethyl acetate = 4:1 or 2nd eluate; acetone = 10:1) of 2 times refined the obtained residue, it recrystallized [mixed solvent / of ethanol and water] and the 2-chloro-4-methyl-4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] nicotine anilide hydrochloride (0.75g) was obtained as non-color powder-like **.

[0033] A WSCD hydrochloride (1.43g) and HOBt (1.10g) were added to an example 74-[3 and 5-bis (trifluoromethyl)-1H-pyrazole-1-IRU] aniline (2.00g) and 3-chloro thiophene-2-carboxylic acid (1.10g) and the mixture of DMF (20ml) one by one under ice-cooling, and it stirred at the room temperature for 20 hours. After adding the WSCD hydrochloride (0.72g) to reaction mixture under ice-cooling and stirring at a room temperature for 4 hours, the 3-chloro thiophene-2-carboxylic acid (0.33g) was added under ice-cooling, and it stirred for one day at the room temperature further. Water (100ml) was added to reaction mixture, and ethyl acetate extracted the product. Sequential washing of the extract was carried out with water, 1 convention hydrochloric acid, water, and saturation brine, and after drying an organic layer with sulfuric anhydride magnesium, it condensed under reduced pressure. After the silica gel column chromatography (n-hexane: eluate; ethyl-acetate = 4:1) refined the obtained residue, it recrystallized [mixed solvent / of ethanol and water] twice, and 3-chloro-4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] thiophene-2-carboxanilide (1.78g) was obtained as a colorless needle shape crystal.

Phosphorus oxychloride (0.006ml) was added to an example 84-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] aniline (15mg) and 5-methylthiophene-2-carboxylic acid (9mg) and the mixture of a pyridine (0.3ml) at -20 degrees C, and it stirred at -20 degrees C for 1 hour. Iced water was filled with reaction mixture and ethyl acetate extracted the product. After carrying out sequential washing of the extract with water, 1 convention sodium-hydroxide water solution, and saturation brine and drying an organic layer with sulfuric anhydride magnesium, it condensed under reduced pressure and 5-methyl-4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] thiophene-2-carboxanilide was obtained.

[0034] HBTU (3.34g) was added to the mixture of an example 95-methyl-2-trifluoromethyl furan-3-carboxylic acid (1.58g), triethylamine (1.4ml), and DMF (20ml), and it stirred for 30 minutes at the room temperature. After adding 4-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] aniline (2.00g) to reaction mixture and stirring for four days at a room temperature, water (150ml) was added to reaction mixture, and ethyl acetate extracted the product. Sequential washing of the extract was carried out with water, a saturation sodium-hydrogencarbonate water solution, and saturation brine, and after drying an organic layer with sulfuric anhydride magnesium, it condensed under reduced pressure. the crystallization from ethyl acetate after a silica gel column chromatography (n-hexane: eluate; ethyl-acetate = 4:1) refines the obtained residue, and the mixed solvent of n-hexane -- subsequently -- from the mixed solvent of ethanol and water -- recrystallizing -- the 5-methyl -2 - trifluoromethyl-4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] furan-3-carboxanilide (2.13g) was obtained as a colorless needle shape crystal.

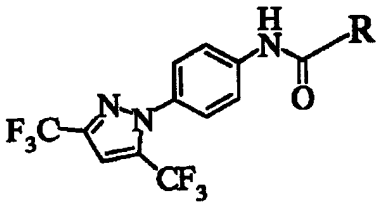
[0035] The mixture of the 6-chloro-4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] nicotine anilide (22mg) compounded by the same approach as example 10 example 9, a morpholine (87mg), potassium carbonate (14mg), and isopentyl alcohol (0.2ml) was stirred at 100 degrees C for 3 hours. A morpholine (44mg) and potassium carbonate (14mg) were added to reaction mixture, and it stirred at 100 degrees C for 1 hour. Water was added to reaction mixture and ethyl acetate extracted the product. It condensed under reduced pressure of an extract and the obtained residue was dissolved in dichloromethane. Insoluble matter was filtered out, after adding PS-isocyanate (the product made from Argonaut Technologies, 1.64 mmol/g) to this thing and making a superfluous morpholine react. It condensed under reduced pressure of filtrate and the 6-morpholino-4'-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] nicotine anilide was obtained.

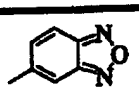
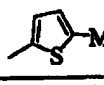
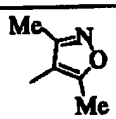
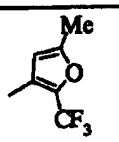
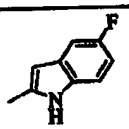
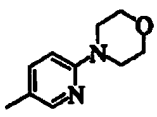
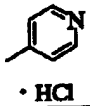
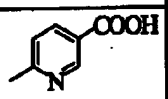
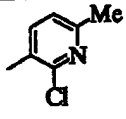
[0036] Methyl compounded by the same approach as example 11 example 9 6-(N-{4-[3 and 5-bis (trifluoromethyl)-1H-pyrazole-1-IRU] phenyl} carbamoyl) NIKOCHINATO (43mg), 1 convention sodium-hydroxide water solution (1ml), and the mixture of 1,4-dioxane (1ml) were stirred at the room temperature for 1 hour. After making acidity or alkalinity of reaction mixture into acidity (pH2) by adding 1 convention hydrochloric acid to reaction mixture, 1,4-dioxane was distilled off under reduced pressure. After separating the depositing solid-state and washing with water, it dried under reduced pressure and 6-(N-{4-[3 and 5-bis(trifluoromethyl)-1H-pyrazole-1-IRU] phenyl} carbamoyl) nicotinic acid was obtained.

[0037] The compound shown in the after-mentioned tables 2-6 like the above-mentioned example was obtained. as physicochemical to the after-mentioned tables 1-6 as the structure expression

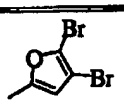
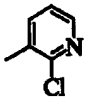
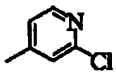
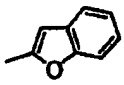
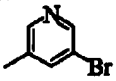
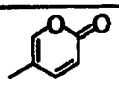
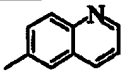
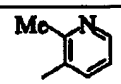
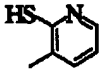
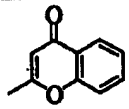
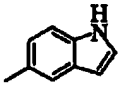
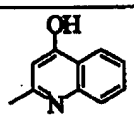
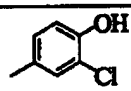
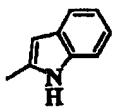
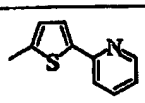
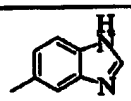
of an example compound -- description is shown, respectively. Moreover, using a suitable raw material compound, almost like an approach given in said example or manufacturing method, the compound [thing mentioned above / tables 7-12 / a compound / a chemical structure type] applies some strange method obvious to this contractor at them, or is manufactured easily. The code below the inside of a table is an Ex:example Sy:manufacturing method (a figure shows the number of said example).; having manufactured the compound concerned by the same approach as said this example is shown. ;Dat: -- physicochemical -- description () [F:FAB-MS] (M+H) -- +; M: -- the melting point [**]; (d): -- decomposition; -- characteristic peak deltappm of N1:NMR (DMSO-d6, TMS internal standard); a part for holding-time [on HPLC in the H1:following HPLC conditions 1] [--]; a part for holding-time [on HPLC in the H2:following HPLC conditions 2] [--];TFA: -- trifluoroacetic acid ; and Co: A compound number is shown, respectively.
HPLC -- conditions -- one -- : -- a column -- : -- Wakosil-II -- five -- C -- 18 -- AR -- 4.6 -- x -- 30 -- mm -- detection -- wavelength -- : -- 254 -- nm -- a column -- temperature -- : -- 35 -- degree C -- the rate of flow -- : -- 4.0 -- mL/min -- an eluate -- : -- five -- mM TFA -- methanol solution -- /-- five -- mM TFA -- a water solution -- = -- ten -- /-- 90 -- < -- zero -- min -- > -100 / 0 <7.5min:straight-line inclination>-100 / 0 <8.0min -- > .
HPLC -- conditions -- two -- : -- a column -- : -- Wakosil-II -- five -- C -- 18 -- AR -- 2.0 -- x -- 30 -- mm -- detection -- wavelength -- : -- 254 -- nm -- a column -- temperature -- : -- 35 -- degree C -- the rate of flow -- : -- 1.2 -- mL/min -- an eluate -- : -- five -- mM TFA -- methanol solution -- /-- five -- mM TFA -- a water solution -- = -- ten -- /-- 90 -- < -- zero -- min -- > -100 / 0 <7.5min:straight-line inclination>-100 / 0 <8.0min -- > .

[0038]
[A table 1]

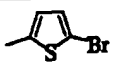
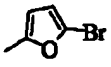
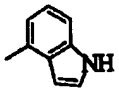
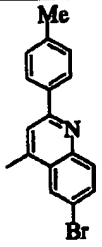
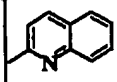
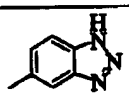
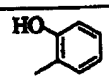
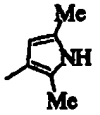
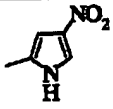
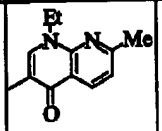
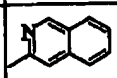
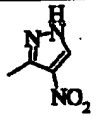
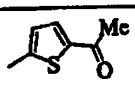
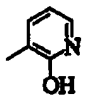
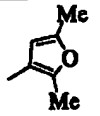
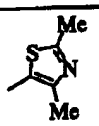
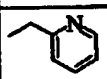
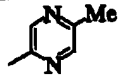
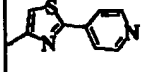
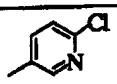
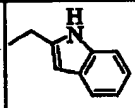


Ex	R	Dat	Ex	R	Dat
1		H1:4.83 F:442	7		M:136-138 ; N1:7.25(1H, d, J=5.3 Hz), 7.96(1H, d, J =4.9Hz)
2		H1:4.92 F:406	8		H1:4.92 F:420
3		M:181-183 ; N1:2.36(3H, s), 2.58 (3H, s)	9		M:148-150 ; N1:2.42(3H, s)
4		H1:5.39 F:457	10		H1:4.35 F:486
5	 · HCl	M:170-172 ; N1:8.19(2H, d, J=5.9 Hz)	11		H1:5.18 F:445
6		M:162-163 ; N1:7.44(1H, d, J=7.8 Hz), 8.02(1H, d, J=7.9Hz)			

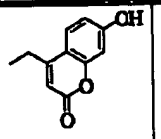
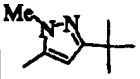
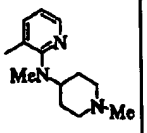
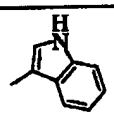
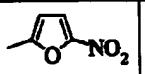
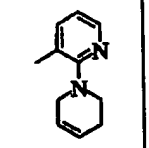
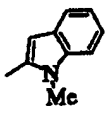
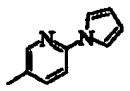
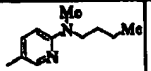
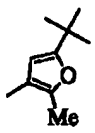
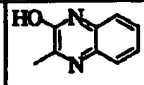
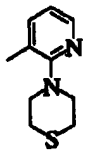
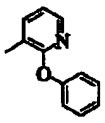
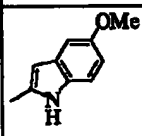
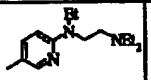
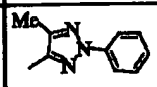
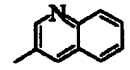
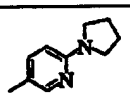
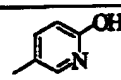
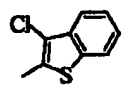
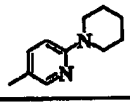
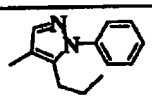
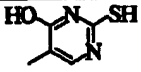
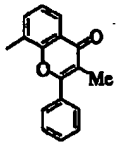
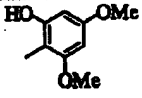
[0039]
[A table 2]

Ex	Sy	R	Dat	Ex	Sy	R	Dat
12	9		M:133-135; N1:7.67(1H, s)	23	5		H1:4.49 F:390
13	5		M:212-213; N1:7.01-7.03(1H, m), 7.81-7.84(2H, m), 8.43-8.44 (1H, m)	24	7		H1:4.40 F:408
14	9		M:154-157; N1:7.60(1H, dd, J=7.9, 4.9Hz), 8.15(1H, dd, J=7.8, 2.0Hz),8.57 (1H, dd, J=4.9, 1.9Hz)	25	7		H1:4.37 F:391
15	9		M:189-190; N1:7.90(1H, dd, J=4.9, 1.5Hz), 8.03(1H, d, J=1.0Hz), 8.65 (1H, d, J=5.8Hz)	26	9		H1:5.20 F:440
16	6		M:169-170; N1:8.58(1H, t, J=2.0Hz), 8.94(1H, d, J=2.0Hz), 9.09 (1H, d, J=1.9Hz)	27	9		H1:4.12 F:418
17	5		H1:4.18 F:451	28	5		H1:3.72 F:415
18	9		H1:5.14 F:433	29	9		H1:5.22 F:468
19	9		H1:3.93 F:439	30	9		H1:5.10 F:467
20	9		M:169-170; N1:7.29(1H, dd, J=7.8, 4.9Hz), 7.98(1H, dd, J=7.8, 1.5Hz),8.62 (1H, dd, J=4.9, 1.5Hz)	31	9		H1:4.11 F:451
21	5		H1:4.99 F:406	32	5		H1:5.06 F:439
22	6		H1:5.21 F:483	33	9		H1:4.11 F:440

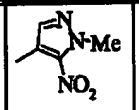
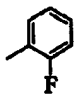
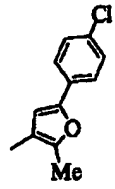
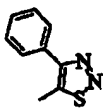
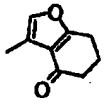
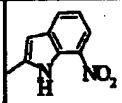
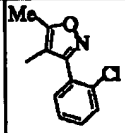
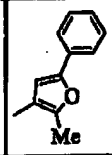
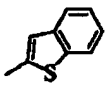
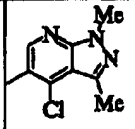
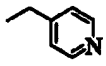
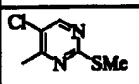
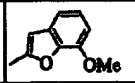
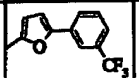
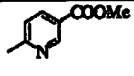
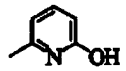
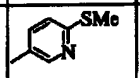
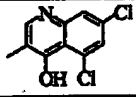
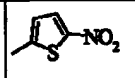
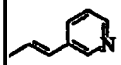
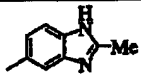
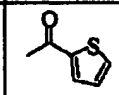
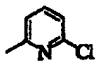
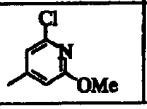
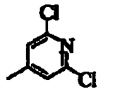
[0040]
[A table 3]

Ex	Sy	R	Dat	Ex	Sy	R	Dat	Ex	Sy	R	Dat
34	6		H1:5.58 F:484	42	9		H1:4.95 F:468	50	9		H1:3.85 F:439
35	6		H1:6.53 F:619	43	9		H1:5.51 F:451	51	9		H1:4.85 F:434
36	6		H1:4.26 F:416	44	6		H1:4.28 F:417	52	6		H1:4.93 F:434
37	9		H1:5.61 F:510	45	9		H1:5.52 F:451	53	6		H1:4.60 F:435
38	6		H1:5.04 F:448	46	9		H1:4.48 F:417	54	6		H1:5.40 F:418
39	6		H1:5.02 F:435	47	9		H1:3.45 F:415	55	6		H1:5.03 F:416
40	9		H1:2.98 F:404	48	9		H1:4.76 F:420	56	9		H1:4.34 F:484
41	9		H1:4.80 F:435	49	4		H1:4.69 F:389	57	9		H1:4.84 F:453

[0041]
[A table 4]

Ex	Sy	R	Dat	Ex	Sy	R	Dat	Ex	Sy	R	Dat
58	6		H1:4.55 F:498	67	5		H1:5.47 F:460	76	10		H1:3.81 F:527
59	4		H1:5.12 F:439	68	5		H1:4.70 F:435	77	10		H1:4.94 F:482
60	5		H1:5.58 F:453	69	5		H1:5.20 F:466	78	10		H1:4.51 F:486
61	4		H1:6.04 F:460	70	4		H1:5.01 F:468	79	10		H1:5.12 F:502
62	6		H1:5.43 F:493	71	4		H1:5.28 F:469	80	10		H1:4.83 F:544
63	6		H1:5.98 F:481	72	5		H1:4.70 F:451	81	10		H1:3.66 F:470
64	4		H1:4.44 F:417	73	6		H1:5.94 F:490	82	10		H1:4.27 F:484
65	6		H1:5.30 F:508	74	4		H1:480 F:450				
66	6		H1:5.70 F:558	75	6		H1:5.85 F:476				

[0042]
[A table 5]

Ex	Sy	R	Dat	Ex	Sy	R	Dat	Ex	Sy	R	Dat
83	7		H1:4.53 F:449	92	6		H1:5.08 F:418	101	7		H1:6.08 F:514
84	7		H1:5.24 F:484	93	6		H1:4.51 F:418	102	7		H1:5.20 F:458
85	7		H1:5.46 F:484	94	6		H1:4.58 F:405	103	3		H1:4.98 F:515
86	3		H1:5.66 F:480	95	6		H1:5.27 F:456	104	3		H1:4.96 F:503
87	6		H1:3.26 F:415	96	9		H2:5.94 F:482	105	6		H1:5.39 F:470
88	6		H1:5.86 F:534	97	9		H2:5.89 F:459	106	6		H1:4.39 F:417
89	6		H1:3.78 F:433	98	9		H2:6.58 F:535	107	6		H1:4.94 F:451
90	6		H1:3.67 F:427	99	9		H2:4.48 F:454	108	6		H1:4.86 F:434
91	9		H2:5.95 F:435	100	9		H2:6.15 F:465	109	6		H1:5.44 F:469

[0043]
[A table 6]

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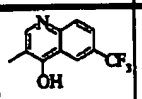
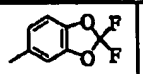
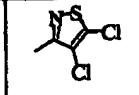
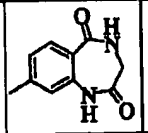
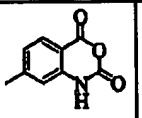
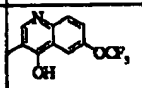
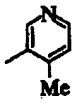
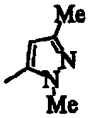
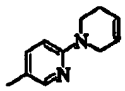
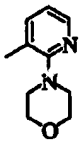
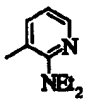
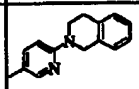
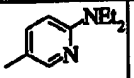
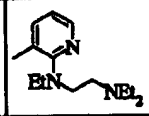
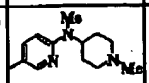
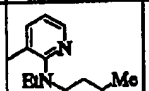
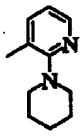
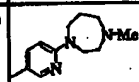
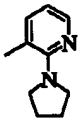
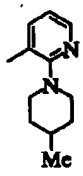
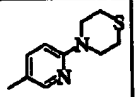
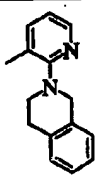
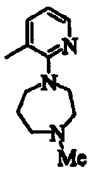
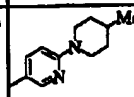
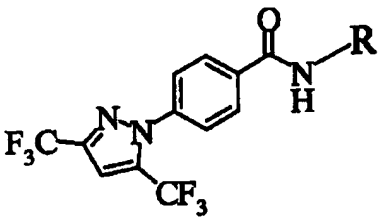
110	9		H2:6.53 F:535	118	9		H2:6.20 F:480	126	9		H2:6.09 F:475
111	9		H2:4.87 F:498	119	9		H2:5.62 F:485	127	9		H2:6.58 F:551
112	9		H2:4.72 F:415	120	9		H2:5.52 F:418	128	10		H1:4.44 F:482
113	10		H1:4.64 F:486	121	10		H1:4.56 F:472	129	10		H1:5.03 F:532
114	10		H1:4.86 F:472	122	10		H1:4.08 F:544	130	10		H1:4.81 F:527
115	10		H1:4.74 F:486	123	10		H1:4.87 F:484	131	10		H1:3.65 F:513
116	10		H1:4.02 F:470	124	10		H1:5.16 F:498	132	10		H1:4.78 F:502
117	10		H1:5.48 F:532	125	10		H1:3.84 F:513	133	10		H1:4.64 F:498

[0044]
[A table 7]



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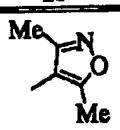
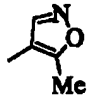
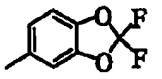
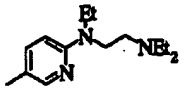
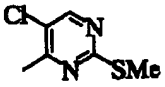
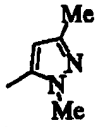
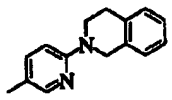
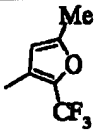
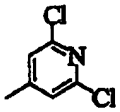
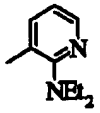
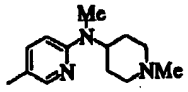
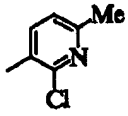
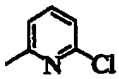
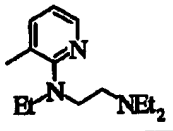
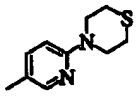
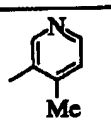
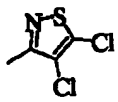
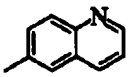
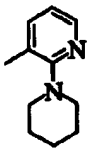
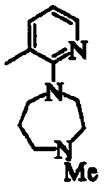
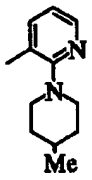
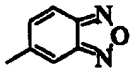
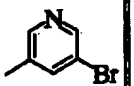
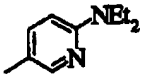
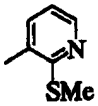
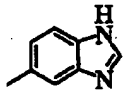
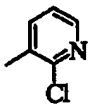
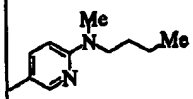
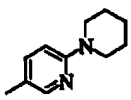
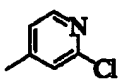
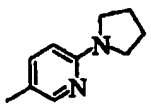
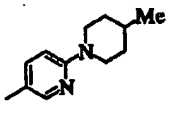
1		10		19		28	
2		11		20		29	
3		12		21		30	
4		13		22		31	
5		14		23		32	
6		15		24		33	
7		16		25		34	
8		17		26			
9		18		27			

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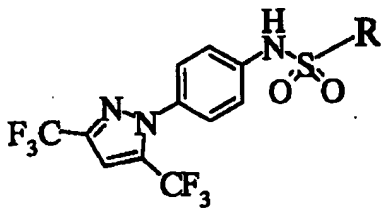

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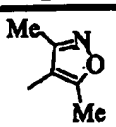
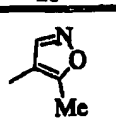
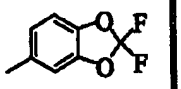
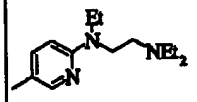
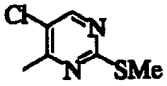
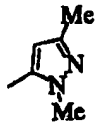
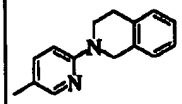
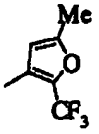
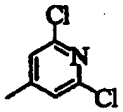
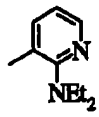
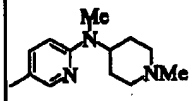
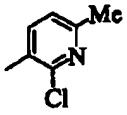
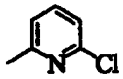
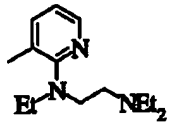
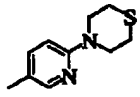
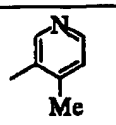
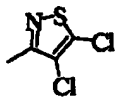
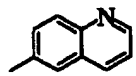
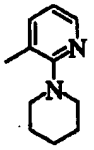
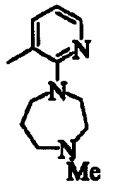
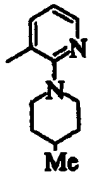
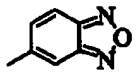
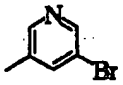
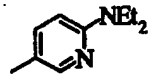
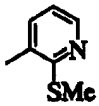
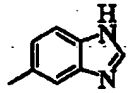
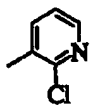
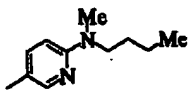
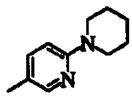
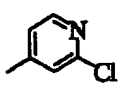
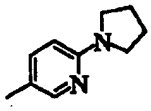
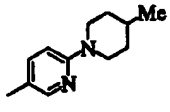
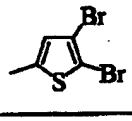
35		44		53		62	
36		45		54		63	
37		46		55		64	
38		47		56		65	
39		48		57		66	
40		49		58		67	
41		50		59		68	
42		51		60		69	
43		52		61		70	

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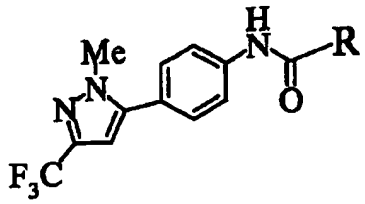

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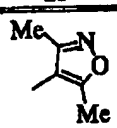
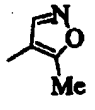
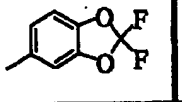
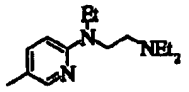
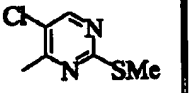
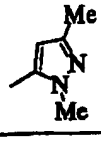
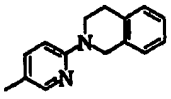
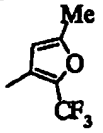
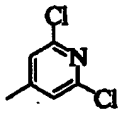
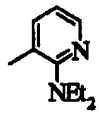
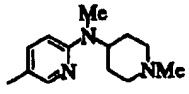
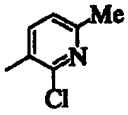
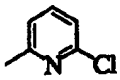
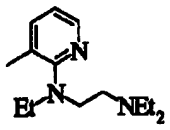
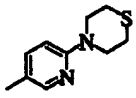
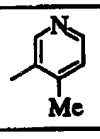
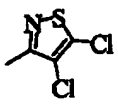
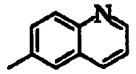
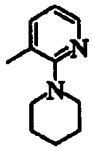
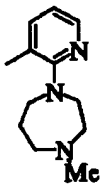
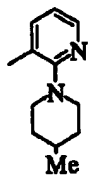
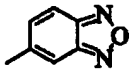
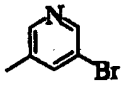
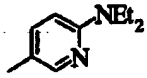
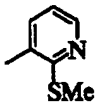
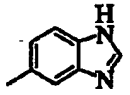
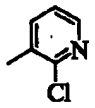
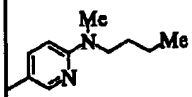
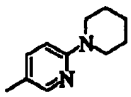
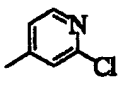
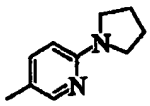
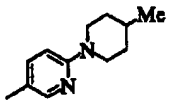
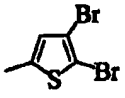
71		80		89		98	
72		81		90		99	
73		82		91		100	
74		83		92		101	
75		84		93		102	
76		85		94		103	
77		86		95		104	
78		87		96		105	
79		88		97		106	

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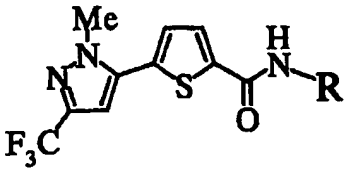

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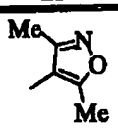
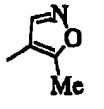
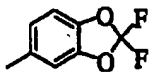
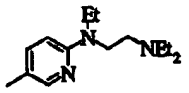
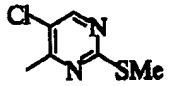
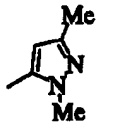
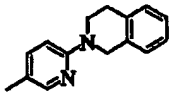
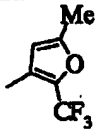
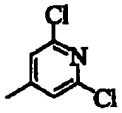
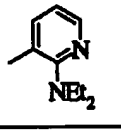
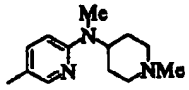
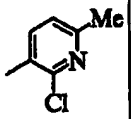
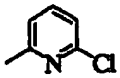
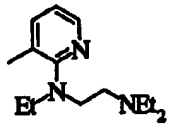
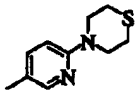
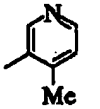
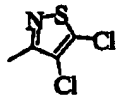
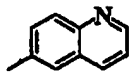
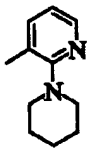
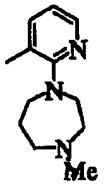
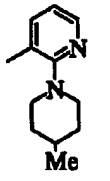
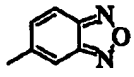
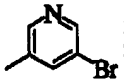
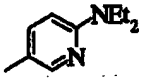
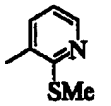
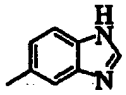
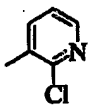
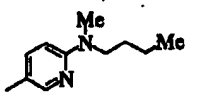
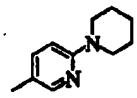
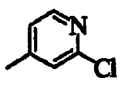
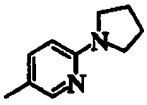
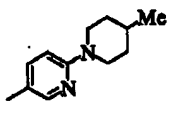
107		116		125		134	
108		117		126		135	
109		118		127		136	
110		119		128		137	
111		120		129		138	
112		121		130		139	
113		122		131		140	
114		123		132			
115		124		133			

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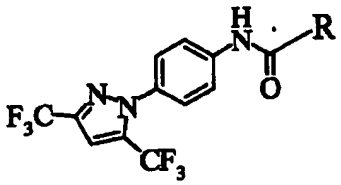

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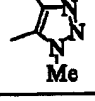
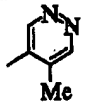
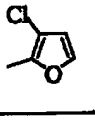
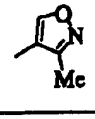
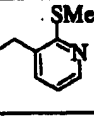
141		152		163		174	
142		153		164		175	
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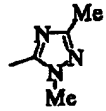
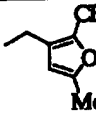
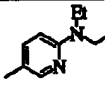
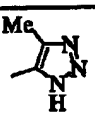
144		155		166		177	
145		156		167		178	
146		157		168		179	
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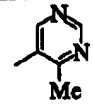
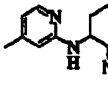
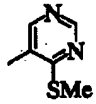
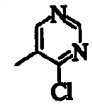
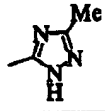
148		159		170		181	
149		160		171		182	
150		161		172		183	
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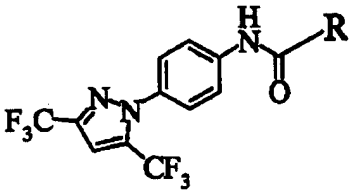

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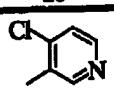
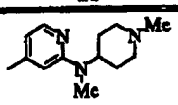
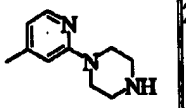
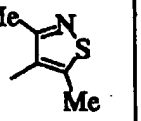
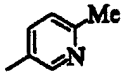
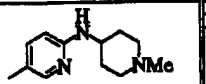
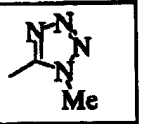
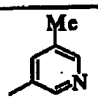
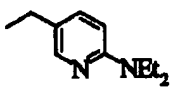
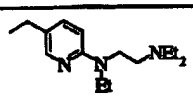
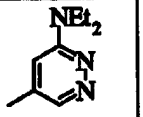
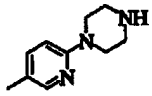
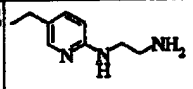
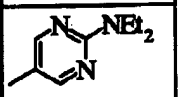
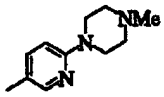
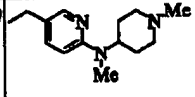
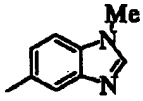
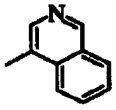
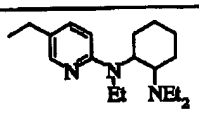
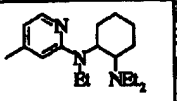
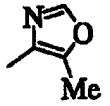
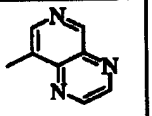
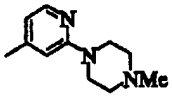
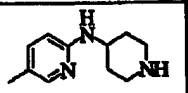
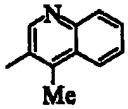
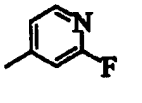
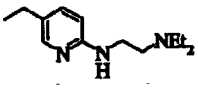
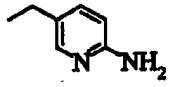
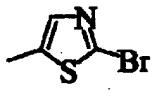
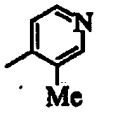
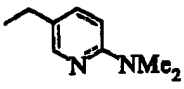
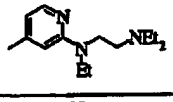
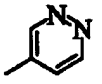
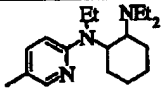
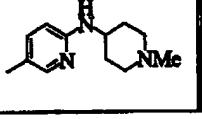
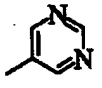
185		195		205		215	
186		196		206		216	
187		197		207		217	
188		198		208		218	
189		199		209		219	
190		200		210		220	
191		201		211		221	
192		202		212		222	
193		203		213			
194		204		214			

[Translation done.]